UM-CDG-088 Special Histochemical and Immunohistochemical Stains	Approved By: Director, Health Services	Effective Date: 10/20/2025

This Policy applies to all SECUR affiliates, associates, and subsidiaries.

Approved by Courtney Gonzales, Director of Health Services on behalf of the Utilization Management Committee.

PURPOSE

This coverage determination guideline serves to address special histochemical and immunohistochemical stains. This coverage determination guideline does not designate specific special histochemical stains (aka special stains) and/or immunohistochemical (IHC) stains that should be used in the differential diagnosis of tissues or neoplasms because this information is readily available in textbooks and various scientific publications. There is no attempt in this coverage determination guideline to be an all-inclusive catalogue for special and immunohistochemical stains. It identifies the medically necessary criteria for the use of special stains and/or IHC stains and addresses, based on claims review, the scenarios that may be driving medically unnecessary over-utilization or incorrect billing of these services.

For SECUR Health Plan members, National Coverage Determinations (NCD) and Local Coverage Determinations (LCD) will be applied to requests when applicable. SECUR Health Plan Coverage Determination Guidelines (CDG) will be utilized in the absence of an appropriate NCD and/or LCD.

DEFINITIONS

None

POLICY

SECUR Health Plan recognizes that the surgical pathology report is expected to designate the specific block(s) upon which IHC testing is performed, the reason and results for IHC testing, the specific markers, and whether single antibody or a cocktail of antibodies is utilized. A statement alone in the pathology report that states, "IHC confirms the diagnosis" will *not be covered* as reasonable and necessary.

There are many different relationships that exist in the provision of pathology services in the United States. It is the obligation of each party to recognize that they are responsible for the medical necessity of the services submitted. For example, when a physician or physician group performs the professional component of services described in this policy and another entity performs the technical services, it is the obligation of each entity to independently assure the medical necessity of the services rendered by each entity.

Special Stains/IHC Medical Necessity

The CMS Internet-Only Manual, Pub. 100-02, Medicare Benefit Policy Manual, Chapter 15, §80.6.5 specifies "…there may be additional tests, such as special stains, that the pathologist may need to perform, even though

they have not been specifically requested by the treating physician/practitioner. The pathologist may perform such additional tests under the following circumstances:

- Services are medically necessary so that a complete and accurate diagnosis can be reported to the treating physician/practitioner;
- Results of the tests are communicated to and are used by the treating physician/practitioner in the treatment of the beneficiary; and
- Pathologist documents in their report why additional testing was done."

The above citation means that reflex templates or pre-orders for special stains and/or IHC stains prior to review of the routine H&E stain by the pathologist are not reasonable and necessary. A pathologist must first review the H&E stain prior to ordering special stains or IHC.

Exceptions do exist and are recognized standards of care in the practice of pathology. These exceptions include but are not limited to renal, liver, and neuromuscular biopsies, and for the suspicion of an infectious disease, particularly in an immune compromised patient. In certain clearly defined circumstances, it may be reasonable to perform some IHC on sentinel lymph nodes when the frozen sections show they are free of tumor.

The medical necessity for the special stain or IHC studies, and the results of the stain or IHC, must be documented in the surgical pathology report.

IHC for Breast Pathology

Ki-67 (MIB-1) has prognostic value in the population of patients with ER+, HER2- lymph node positive high risk breast cancer for use of the Cyclin-dependent 4 and 6 (CDK 4/6) inhibitor abermaciclib (Eli Lilly and Company) as adjuvant therapy in addition to endocrine therapy. Outside of this exception, Ki-67 is not considered reasonable and necessary for breast cancer and consequently will not be covered by Medicare.

In the absence of professional guidelines based on proven scientific literature, standing orders from clinicians for such tests as Ki-67 and epidermal growth factor receptor (EGFR) on every breast cancer are not reasonable and necessary and are not a covered Medicare service.

Special Stains and/or IHC for Gastrointestinal (GI) Pathology

Only the pathologist may determine the need for a special stain. Ordering special stains or IHC stains on every specimen prior to review of the routine H&E stain is not reasonable and necessary.

Other examples of special stains or IHC that are not reasonable and necessary on every specimen include:

- Esophagus – fungal stains, trichrome, diastase-PAS (D-PAS), CDX-2 or other mucin stains.
- Gastric – alcian blue/periodic acid-Schiff (AB-PAS), D-PAS, CDX-2 or other mucin stains, or special stains or IHC for Helicobacter pylori (H. pylori), or neuroendocrine markers such as synaptophysin or chromogranin.
- Duodenum – AB-PAS, D-PAS, CD3, and trichrome, or other mucin stains;
- Colon – CD3, p53 trichrome.
- Hyperplastic polyps – Ki-67, CK20, p53, CEA, BRAF; and
- Tubular or tubulovillous adenoma – Ki-67, CK20, CEA, p53, mismatch repair (MMR).

If special stains or IHC are needed in addition to the routine H&E for gastric specimens, specific documentation to justify the medical necessity for the stain is required in the pathology report. Cases that may require special stains or IHC include but are not limited to the following:

- Detection of H. pylori in an appropriate milieu when organisms are not seen on H&E stained slides.
- Evaluating atrophic gastritis for evidence of autoimmune etiology and for enterochromaffin-like (ECL) cell hyperplasia/carcinoid tumor.
- Characterizing a carcinoma, lymphoma, melanoma or sarcoma.

- Defining a gastrointestinal stromal tumor (GIST) and to distinguish it from mimics; and
- Ki-67 by IHC in the differential diagnosis of certain neuroendocrine tumors of the gut.
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Special Stains and/or IHC for Prostate Pathology

It is not reasonable and necessary to routinely perform IHC testing (either single antibody or antibody cocktails) on cases with morphologically negative cores. The pathologist may choose to confirm a suspicious focus in 1 or more cores in a case irrespective of carcinoma in other cores. However, there must be reasonable and necessary documentation that the volume, multifocality or additional findings in lower-grade tumor positive biopsies will influence treatment decisions, prognosis or have other clinical implications per the NCCN Guidelines Version 1, 2023 Prostate Cancer (27). It is not a Medicare covered service if the results of immunohistochemical stains does not provide additional actionable information to the treating physician.

Prostate cases that may require reasonable and necessary IHC staining include but are not limited to the following:

- Indeterminate/suspicious focus and no other cores are positive for cancer.
- Single worrisome core with minimal % tumor (roughly <5%).
- Worrisome core(s) contralateral to a positive core(s):
    - In a multi-part biopsy with Gleason 3+3=6 cancer in 1 part, and atypical small acinar proliferation (ASAP) suspicious for Gleason 3+3=6 cancer in other part(s); the number of positive biopsy sites and % core involvement of these sites can affect therapeutic choices for active surveillance (AS), focal therapy or surgery
    - In a multi-part biopsy with 4+3=7 or 4+4=8 cancer in 1 part, and ASAP suspicious for the same grade cancer in other part(s); workup is justified since the extent of high-grade cancer affects treatments.
- Identify tumor invasion of adjacent structures.
- Determine origin of undifferentiated/poorly differentiated neoplasm, such as bladder vs. prostate; and
- Other unexpected results when specific cell stains would be necessary.
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Special Stains and/or IHC for Lung Cancer

The diagnostic challenge of a lung biopsy can often prompt the need for additional stains to define the neoplasm. However, the use of an excessive number of stains where results do not document their significance to provide actionable information are not reasonable and necessary.

The diagnosis of small cell and non-small cell carcinoma often requires additional stains but it is essential that tumor tissue be carefully triaged to allow the patient's sample to be evaluated for molecular markers (i.e., EGFR, ALK, and others) when clinically indicated.

IHC for Predictive Marker Tumor Profiling

Estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor (Her2) testing for the purpose of identifying patients likely to respond to hormonal therapy, biologics or chemotherapy is a covered Medicare service when medically necessary for breast and gastric adenocarcinoma.

Chemosensitivity profile tumor panels, regardless of whether it is performed by IHC or chromogenic in-situ hybridization (CISH), is not reasonable and necessary and is not a Medicare covered service.

IHC for Cervical/Gyn/Bladder/Kidney Tumors

A variety of IHC stains have found limited use in cervical, gynecologic, and urologic tumor settings. In unusual cases of cervical dysplasia, markers or surrogate markers for HPV may be useful where the diagnosis on conventional H&E stain cannot be made with certainty. These markers are clearly not reasonable and necessary on

all biopsies.
In renal neoplasms IHC stains such as CK7, CK20, CAIX, CD10, CD117, PAX2, PAX8 (33) among many can be used for accurate classification of renal neoplasms, both on core biopsy and on resection. Core biopsies are often performed in patients for whom surgery is not an acceptable option due to known comorbidities and other potential risks/complications, or for tumors that may need treatment prior to surgery and therefore accurate diagnosis on biopsy is crucial. Renal neoplasia entities or groups of entities are increasingly characterized by specific molecular features, often associated with either recognizable, specific morphologies or constellations of morphologies and corresponding immunohistochemical profiles. The correct diagnosis has clinical implications leading to more accurate prognosis, potential clinical management with targeted therapies and may identify hereditary or systemic associations.
There are morphologic features that are diagnostic of certain histologic types of tumors but similar growth patterns or cytologic features can be seen in a variety of tumor types. Thus, the rationale for IHC staining use should be properly documented as reasonable and necessary to resolve situations regarding the possible differential diagnoses.

IHC for Skin & Cutaneous/Central Nervous System (CNS) & Peripheral Nervous System (PNS) Lesions
Most skin lesions are diagnosed with routine H&E slides. A minority of skin lesions require immunostains (e.g., atypical fibroxanthomas, Merkel cell lesions, lymphomas). Most common skin lesions (e.g., seborrheic keratosis) do not require IHC stains. Use of IHC morphometric codes for skin lesions is not reasonable and necessary unless under rare instances.
Many central nervous system (CNS) and peripheral nervous system (PNS) lesions are readily diagnosed with routine stains. However, recent classifications use defined molecular biomarkers as well as immunostains to identify and define specific lesions.

IHC for Bone Marrow Samples
Most bone marrow samples are diagnosed with the use of Wright's-stained smears and the use of H&E stained slides with an iron stain supplementing the battery. The use of IHC stains may assist in the interpretation of cases where flow cytometry (FC) does not fit with the routine slide interpretation, when FC was not obtained or for the evaluation of cell types that are not detected or significantly underrepresented in FC studies, such as large lymphocytes, plasma cells and Reed-Sternberg cells. IHC stains are not needed to confirm the results of FC and cytogenetic studies. When medically indicated, justification for the use of both methods must be stated in the pathology report and billed accordingly.

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